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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	AIB-08252	2472

23535 7590 07/07/2010

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
07/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 17, 2010 has been entered.

Claims 1-39, 41, 43, 45, 47-55, 59, 60 are cancelled.

Claims 40, 42, 44, 46, 56-58, 61, drawn to a drawn to a composition comprising milk derived from a transgenic mammal and a recombinant human prothrombin, wherein the Gla domain of prothrombin is gamma-carboxylated, are under consideration.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10,

1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, Seegers et al., 1950, Blood, 5: 421-433, previously cited, van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010.

Claims 40, 42, 44, 46, 56, and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010.

Claims 40 and 57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, in view of Seegers et al., 1950, Blood 5: 421-433, previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010.

Applicant's arguments filed May 17, 2010 have been fully considered but they are not persuasive.

It is noted that Applicant's response of May 17, 2010 appears to be a substantial duplicate of the response provided by Applicant on December 29, 2009. As such, the Examiner's response, February 19, 2010, is reiterated as follows. Response to Applicant's newly added argument follows the text copied from February 19, 2010.

With regard to the Examiner relying on Meade et al. for teaching an efficient means of making large quantities of recombinant protein in milk (Office Action, Sept, 2009, page 4), Applicant indicates that Meade et al. uses the term "large quantities" only once to frame a goal that has advantages of cell culture secretions. Meade et al. col. 1, lines 53-56. Meade et al. failed to produce any method that, in fact, produces large quantities of recombinant protein (the G1 progeny produced 0.2-0.5 ug/ml of TPA in their milk, Meade et al. col. 7, lines 25-26) (Applicant's response, page 5). In response, this is not persuasive. Meade et al.'s working example is not indicative that an artisan would have been limited to make recombinant protein in mice and that transgenic mammals can only make a maximum of 0.5 ug/ml of protein in milk. For example, it is noted that Velander et al., 1992 teach that one transgenic pig produced 1000ug/ml (i.e., 1 mg/ml) of recombinant protein into milk.

Applicant indicates that the primary combination of Meade et al. and Jorgensen et al. do not teach any high level expression of a recombinant protein, and the Examiner now agrees that Jorgensen et al. also do not provide any teachings relevant for high expression of a recombinant protein. Applicant indicates that the Federal Circuit has long since ruled that a specific teaching within a cited reference cannot be considered in isolation when determining obviousness, Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1556, 225 USPQ 26 (Fed. Circ. 1985) (Applicant's response, pages 5-6). In response, this is not persuasive. With regarding to Applicant indicating that Jorgensen et al. do not teach high levels of expression, Applicant is correct. Jorgensen et al. teach expression of prothrombin in Chinese hamster ovary (CHO) cells. The Examiner has not ignored this issue in the obviousness rejection because Jorgensen et al.'s teaching of low production in CHO cells is motivation for an artisan to produce recombinant

protein in milk, wherein expression of recombinant protein in milk is higher than CHO cells (e.g. see Meade et al. and Velander et al.).

With regard to the Examiner's use of Velander et al. for allegedly fulfilling the above deficiencies of Meade et al. and Jorgensen et al., Applicant indicates that the Examiner may have misunderstood the assay systems disclosed within Velander et al. In brief, the Examiner may have overlooked that Velander has reported the detection of 1000 ug/ml of hPC antigen. (Protein Analysis, Antigen levels detected by ELISA using polyclonal capture ranged from 200 ug/ml to 1000 ug/ml; Velander et al., page 12005, 1st col., parag. under "Protein Analysis"). Velander et al. teach that hPC antigen measurements are not equivalent to the detection of an intact, fully carboxylated active hPC, see Velander et al. page 12007, col., last 2 parags. In summary, Velander et al. i) teach assays for total hPC antigen, that represents 38% active and 62% inactive hPC protein and ii) does not teach the secretion of 1 mg/ml of a fully carboxylated recombinant protein (see Velander declaration) (Applicant's emphasis, Applicant's response, pages 6-7). In response, this is not persuasive. While Velander et al. teach that 38% of hPC was gamma-carboxylated, this is not indicative that all gamma-carboxylated proteins have the same level of gamma-carboxylation. Camire et al., 2000, Biochemistry, 39: 12433-14329 teach that the affinities of vitamin K-dependent propeptides for gamma-carboxylase vary over 2 logs, with factor X having the highest affinity and prothrombin having the lowest. Camire et al. teach that this difference is localized to the 18 amino acid propeptide region of these proteins. Camire et al. teach that when the propeptide region of prothrombin was fused with factor X, 85% of the total factor X was fully gamma-carboxylated, compared with 32% of native factor X (Camire et al., abstract). As such, Camire et al.'s teaching is indicative that 85% gamma-carboxylation is an inherent property of prothrombin. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

With regard to the citation of Seegers et al., Applicant indicates that Seegers et al. does not remedy the deficiencies of Meade et al., Jorgensen et al., and Velander et al. by teaching a

highly expressed fully carboxylated recombinant protein (Applicant's response, pages 7-8). In response, this is not persuasive. As indicated above, Meade et al., Jorgensen et al., and Velander et al. provide guidance for an artisan to make large amounts of recombinant prothrombin in the milk of mammals. Also, as indicated above, 85% of the prothrombin produced in milk being gamma-carboxylated is an inherent characteristic of prothrombin.

With regard to the citation of van Cott et al., Applicant indicates that the Examiner has ignored that van Cott et al. do not teach a fully-gamma carboxylated recombinant protein at a level of 0.5 mg/ml, see the Velander Declaration (Applicant's response, page 8). In response, this is not persuasive. As indicated above, Meade et al., Jorgensen et al., and Velander et al. provide guidance for an artisan to make large amounts of recombinant prothrombin in the milk of mammals. Also, as indicated above, 85% of the prothrombin produced in milk being gamma-carboxylated is an inherent characteristic of prothrombin.

With regard to the citation of Le Bonniec et al., Applicant indicates that Le Bonniec et al. do not remedy the lack of a prima facie case of obvious in view of the other references discussed above. Specifically, Le Bonniec et al. do not teach recombinant prothrombin in the milk of a transgenic mammal having a concentration of at least 0.5 mg/ml (Applicant's response, pages 8-9). In response, this is not persuasive. As discussed above, Meade et al., Jorgensen et al., and Velander et al. provide guidance for an artisan to make large amounts of recombinant prothrombin in the milk of mammals. Also, as indicated above, 85% of the prothrombin produced in milk being gamma-carboxylated is an inherent characteristic of prothrombin.

Applicant indicates that the Examiner attempts to rebut the Velander declaration by presenting the publication by Camier et al., 2000. The Examiner is respectfully requested to note that Camier et al. was published after the Applicant's priority date. As such, Camire et al. is not prior art and is also not a proper teaching reference. Specifically, Camire is an in vitro system as compared to Applicant's claims that recite in vivo production in transgenic

animals. Due to the well accepted unpredictability of the biotechnological arts, Camire et al. do not show an inherent property of prothrombin (Applicant's response, page 9). In response, this is not persuasive. With regard to Applicant indicating that Camire et al., 2000 is post-filing art, it is noted that Camire et al. was cited to further illustrate that a high level of gammma-carboxylation is an inherent property of the propeptide of thrombin. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). With regard to Applicant indicating that Camire et al. teach that their assay was carried out in vitro, while the instant application is drawn to a method carried out in vivo, it is noted that gamma-carboxylation is a property of the property of the propeptide and not a property of the cell and whether or not the cell is in vivo or in vitro. As far as can be told, what influences gamma-carboxylation is the sequence of the propeptide and not the cell type or whether the cell is in vitro or in vivo.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had

been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Primary Examiner
Art Unit 1632